REMARKS

Claim Status

Upon entry of the amendments, claims 2, 3, 8-13, 19-21, 34, 39, and 41-50 constitute the pending claims in the present application. Claims 2, 3, and 46-50 are withdrawn from consideration. Applicants respectfully request rejoinder of the withdrawn species claims upon allowance of a linking claim.

For clarity and antecedent basis, claims 2 and 3 have been amended to refer to a "Purkinje neuron deficiency." Independent claim 34 has been amended. The amendment to claim 34 is supported, at least, by paragraph 11 of the published application (2004-0115175) which recites "The neuronal deficiencies treated by the invention exclude neuronal deficiencies arising from a disorder selected from the group consisting of a lysosomal or peroxisomal disorder..." In addition, support may be found in paragraph 89 which states "The use of granulocyte colony stimulating factor (G-CSF) for bone marrow cell mobilization is well known..." The amendments introduce no new matter.

In addition, Applicants note that the publication Nimgaonkar *et al.* was newly cited by the Examiner in this final office action. This publication could have been cited in a previous office action, as both the current and the previous claim sets referred to G-CSF and Purkinje neuron deficiencies, the subject matter of the novelty rejection in view of Nimgaonkar *et al.* Thus, Applicants traverse the finality of this office action because the rejection based on Nimgaonkar is not necessitated by Applicants' previous claim amendment or IDS submission, and Applicants respectfully request that the Examiner withdraw the finality of the recent Office Action.

Applicants respectfully request reconsideration of the rejections in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Election/Restriction

The Examiner states, on page 2 of the recent Office Action, "The newly amended claims are directed to a method of treating disorders caused by Purkinje neuron deficiency. As such, it appears that none of the diseases listed in claim 2 falls into this category as defined by the specification (paragraph 0105)". Applicants respectfully traverse.

First, upon entry of the claim amendments herein, the claims no longer recite "an individual having a disorder caused by a deficiency of Purkinje neurons" but simply refer to "an individual having a deficiency of Purkinje neurons". Thus, the restriction is moot.

Second, paragraph 0105 reads, in pertinent part, "A loss of Purkinje cells results in deficits in these functions in several disorders: ataxia-telangiectasia, the most common cause of progressive ataxia in infancy; Menkes' Kinky Hair syndrome; the alcoholic cerebellar degenerations, particularly Wernicke-Korsakoff syndrome; and various prion diseases including scrapie, Creutzfeldt-Jakob, and Kuru." This sentence simply provides a non-exhaustive list of diseases in which Purkinje cells are lost. Therefore, claim 2 further limits the scope of the amended claim 34 by specifying the specific disease conditions in said "individual having a deficiency of Purkinje neurons" recited in claim 34. Applicants do not understand why the Examiner states that claim 2 no longer reads on the elected species. Clarification is respectfully requested.

Furthermore, to clarify the subject matter, claim 2 has been amended to specify a "Purkinje neuron deficiency".

Next, the Examiner states that "claim 3 excludes a lysosomal or peroxisomal disorder, which is known to have significant loss of Purkinje neurons in the nerve system" and states that this claim no longer reads on the elected species (page 2). Applicants respectfully traverse. A dependent claim, by definition, may further limit the scope of the independent claim by, for example, provisoing out several classes of Purkinje neuron disorders. Thus, claim 3 is part of the elected claim group. Nevertheless, to clarify the subject matter, claim 3 has been amended to specify a "Purkinje neuron deficiency".

The restriction of claims 2 and 3 was therefore improper, and Applicants respectfully request consideration of claims 2 and 3.

Priority

The Examiner argues that "the disclosure of the prior-filed application, Application No. 09/993,045, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application," (page 3). Applicants respectfully disagree. But since the argument below does not need to rely on the claimed priority date to overcome prior art rejection, Applicants will not address this issue here, but reserve the right to present arguments at a later time if necessary.

Claim rejections under 35 U.S.C. §112, second paragraph, indefiniteness

Claims 8-13, 19-21, 34, 39, and 41-45 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Specifically, the Examiner finds the phrase "a disorder caused by a deficiency of Purkinje neurons" vague and indefinite (page 4). The Examiner also states, "it is unclear what other disorders are caused by a deficiency of Purkinje neurons and embraced by the claims, and thus the metes and bounds of the claims are uncertain" (page 4). Applicants respectfully disagree. Nevertheless, to expedite prosecution, Applicants have amended independent claim 34 to refer to "an individual having a deficiency of Purkinje neurons" rather than "an individual having a disorder caused by a deficiency of Purkinje neurons".

In light of the claim amendments and remarks above, the Examiner's argument becomes moot. Reconsideration and withdrawal of the indefiniteness rejection is respectfully requested.

Claim rejections under 35 U.S.C. §112, first paragraph, enablement (new matter)

Claims 8-13, 19-21, 34, 39, and 41-45 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Specifically, the Examiner states that the instant new matter rejection relates to "the claimed **agent** capable of **inducing** the formation of the Purkinje/bone marrow-derived heterokaryon in the nervous system of the individual, the specification only teaches agents that **mobilize** bone marrow cells," (page 5; emphasis in the original). To clarify the subject matter claimed, Applicants have amended claim 34 to recite "wherein the agent induces mobilization of bone marrow cells which results in the formation of the Purkinje/bone marrow-derived heterokaryon". Applicants submit that the claim as amended does not require that the agent directly induces heterokaryon formation. To further clarify, Applicants have previously provided data and arguments (e.g. in the Office Action Response dated September 9, 2008) supporting the position that increasing the number of bone marrow cells in the circulation promotes the formation of Purkinje/bone marrow cell-derived heterokaryons. To summarize, the specification as-filed teaches that bone marrow transplants and bone marrow cell mobilization therapies are two ways of increasing the number of bone marrow cells in the bloodstream, which in turn promotes the formation of heterokaryons between bone marrow derived cells and Purkinje neurons (see, for example, paragraphs 10 and 15 of the published application).

Accordingly, Applicants submit that the specification fully enabled one of ordinary skill at the art at the time of filing to practice the presently claimed methods. Thus, the present claims do not constitute new matter. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim rejections under 35 U.S.C. §112, first paragraph, enablement (new matter)

Next, claims 8-13, 19-21, 34, 39, and 41-45 are newly rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended. In particular, the Examiner states, "the original disclosure fails to teach 'a disorder *caused* by a deficiency of Purkinje neurons'" (page 6; emphasis in the original).

As mentioned above, Applicants have amended independent claim 34 to refer to "an individual having a deficiency of Purkinje neurons" rather than "an individual having a disorder caused by a deficiency of Purkinje neurons". The specification refers to individuals having a deficiency of Purkinje neurons, for example in paragraph 105 of the published application which states "A loss of Purkinje cells results in deficits in these functions in several disorders: ataxia-telangiectasia, the most common cause of progressive ataxia in infancy; Menkes' Kinky Hair syndrome; the alcoholic cerebellar degenerations, particularly Wernicke-Korsakoff syndrome; and various prion diseases including scrapie, Creutzfeldt-Jakob, and Kuru. Thus, renewal or rescue of Purkinje neurons has significant therapeutic implications."

Applicants believe this rejection is now moot. Reconsideration and withdrawal are respectfully requested.

Claim rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 8-13, 19-21, 34, 39, and 41-45 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The instant claims are directed to "a method for producing a Purkinje/bone marrow-derived heterokaryon" (see claim 34). However, relying on the "broadest reasonable interpretation" standard, the Examiner argues that the "instant claims are directed to treating disorders as listed above (in the specification)." Applicants submit that the Examiner has misinterpreted the "broadest reasonable interpretation" standard, and has impermissibly imported limitations not present in the claims before applying the enablement standard to these non-existing limitations.

As the Examiner is aware, the policy rationale behind the "broadest reasonable interpretation" standard is that "broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)." MPEP 2111. Therefore, under the "broadest reasonable interpretation" standard, the Examiner is to interpret the scope of an existing claim limitation broadly, so long as the interpretation is reasonable in view of the specification. But here, rather than *broadening* claim scope, the Examiner appears to limit claim scope by arguing that the claims are "directed to treating disorders," a limitation that has no basis in the claim.

To illustrate the point, Applicants wish to bring the Examiner's attention to *In re Prater*, 415 F.2d 1393 (CCPA 1969) (MPEP 2111). In *Prater*, claim 9 is directed to a method of analyzing mass spectrometry data using a mathematical manipulation. The Examiner properly interpreted the claim, under the "broadest reasonable interpretation" standard, to include a prior art mental process augmented by pencil and paper markings, and rejected the claim under 35 U.S.C. § 102. In *Prater,* the Applicant apparently argued that the specification teaches the use of a machine to carry out the claimed method. The court agreed with the Examiner that the machine limitation is not in the claim, and explained that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from 'reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that Applicant was advocating the latter, *i.e.*, the impermissible importation of subject matter from the specification into the claim, in order to narrow the claim scope to avoid prior art rejection.

Here, there is no explicitly recited claim limitation such as "treating disorders." Rather, the Examiner is apparently narrowing the scope of claim 34 by implicitly adding this disclosed limitation which has no express basis in the claim. Having narrowed the scope of claim 34, the Examiner then requires Applicants to enable a treatment method that displays "detectable beneficial effect," and rejected the claim by arguing that no beneficial effect can be shown for any of the disease conditions referred to in the Office Action. Applicants respectfully submit that the

enablement rejection based on the non-existing claim limitation is improper and should be withdrawn.

The Examiner also argues that the claims are not enabled because there is no evidence that G-CSF mobilized bone marrow stem cells can induce the formation of heterokaryons. On this subject, the Examiner argues, "the specification fails to provide any evidence that administering G-CSF, or any agent [for] that matter, would induce the formation of new Purkinje neuron[s] in the nerve system," (page 11). However, the art makes clear that G-CSF is sufficient to increase the number of mobilized bone marrow cells. Further, Applicants disclosure as filed makes it clear that increasing the number of mobilized bone marrow cells causes an increase in heterokaryon formation (see, e.g. Example 4). As supporting evidence, the Declaration filed October 31, 2007 shows that transplanting only *one* bone marrow derived cell is sufficient to produce a heterokaryon. Since G-CSF can increase the number of mobilized CD34+ cells by 5-fold, as taught in Nimgaonkar *et al.*, one of skill in the art, in view of the prior art and Applicants' disclosure, would not need to conduct undue experimentation in order to use G-CSF to produce the requisite increase in mobilized bone marrow cells to form a Purkinje/bone marrow-derived heterokaryon. Thus, the totality of evidence at the time of filing, supported by post-filing evidence, indicates that administering G-CSF, or any other bone marrow cell mobilizing agent, would induce the formation of one or more Purkinje/bone marrow-derived heterokaryons.

In fact, bone marrow cell mobilization therapy is an art-accepted alternative to bone marrow transplantation *for the purpose of increasing the number of mobilized bone marrow-derived cells in the bloodstream.* Contrary to the Examiner's assertion, G-CSF was known in the art to increase the number of mobilized bone marrow cells in the bloodstream even in the absence of a bone marrow transplant. For example, in Nimgaonkar *et al.* (cited by the Examiner in the previous office action), the authors treat patients with G-CSF and report "An increase in CD34+ cells in the peripheral blood was noted from day 5 onward (up to a six-fold increase)," (page 1633, column 1). This was in the absence of a bone marrow transplant. Thus, bone marrow cell mobilization therapy is an art-accepted alternative to bone marrow transplantation *for the purpose of increasing the number of mobilized bone marrow-derived cells in the bloodstream.*

Accordingly, Applicants submit that, if the scope of the claim is corrected interpreted, the specification fully enables one of ordinary skill at the art at the time of filing to practice the claimed methods/make and use the claimed systems, and that the present claims are adequately supported by the specification. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim rejections under 35 U.S.C. §102(b)

Claims 34, 39, and 41-45 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Nimgaonkar *et al.* (Exp Hematol 1995; 23:1633-41) as evidenced by Conradi *et al.* (Acta Neuropathol 1984; 65:99-109). Specifically, the Examiner states, "*Nimgaonkar* teaches a method of treating Gaucher disease comprising a step of administering cytokine G-CSF" (page 15). Applicants respectfully traverse the rejection to the extent it is maintained in light of the claim amendments.

As stated in Nimgaonkar *et al.*, "Gaucher disease is the most common human lysosomal storage disorder" (page 1633, column 2). Independent claim 34, as currently amended, recites "wherein said Purkinje neuron deficiency is not a neuron deficiency arising from a lysosomal or peroxisomal disorder." Gaucher disease is excluded from the claim. Consequently, Nimgaonkar *et al.* and Conradi *et al.* do not teach or suggest administering G-CSF to a patient having a Purkinje neuron deficiency that "is not a neuron deficiency arising from a lysosomal or peroxisomal disorder".

Accordingly, Applicants submit that claims 34 is not anticipated by Nimgaonkar *et al.* (Exp Hematol 1995; 23:1633-41) as evidenced by Conradi *et al.* (Acta Neuropathol 1984; 65:99-109). Hence, its dependent claims 2, 3, 39, and 41-45 are also novel. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim rejections under 35 U.S.C. §103(a)

Claims 8-13, 19, 20, and 34 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Nimgaonkar *et al.* (Exp Hematol 1995; 23:1633-41) as evidenced by Conradi *et al.* (Acta Neuropathol 1984; 65:99-109) and Martinez-Murillo *et al.* (Neurosci 1993; 52:587-93).

Nimgaonkar *et al.* and Conradi *et al.* have been addressed above. Martinez-Murillo *et al.* does not remedy the deficiencies of Nimgaonkar *et al.* and Conradi *et al.* Thus, reconsideration and withdrawal of this rejection on ground of 35 USC 103(a) is respectfully requested.

Claim rejections under 35 U.S.C. §103(a)

Claims 19-21, 34, 39, and 41-45 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Sanchez-Ramos *et al.* (WO99/56759) in view of Bodine *et al.* (Blood 1994; 84:1482-91) and Eglitis *et al.* (US Patent 7,022,321). Specifically, the Office Action asserts that Sanchez-Ramos teaches the transplantation of bone marrow cells into the rat brain, where the bone marrow cells allegedly take on the appearance of Purkinje neurons. The Examiner then states that Bodine *et al.* supplements this teaching by establishing that G-CSF stimulates mobilization of bone marrow cells. The Examiner adds, "*Eglitis* supplements *Sanchez-Ramos* in view of *Bodine* by establishing it was known in the art that intravenous injection of bone marrow progenitor cells would cross [the] blood-brain barrier to arrive in the brain" (page 18). Applicants respectfully traverse on the following grounds.

First of all, Applicants respectfully disagree with the notion that Sanchez-Ramos *et al.* teaches the transplantation of "bone marrow cells" into the rat brain. The cells transplanted in Sanchez-Ramos *et al.* are not the bone marrow stem cells mobilized by G-CSF in Bodine *et al.*, nor the bone marrow progenitor cells injected intravenously in Eglitis *et al.*. Rather, they are pre-treated with cis-9 retinoic acid and BDNF. See Sanchez-Ramos *et al.* on page 21, lines 3-4: "[p]rior to grafting, BMSC were treated for 2 days with cis-9 retinoic acid (0.5 μM) and BDNF (10 ng/ml)" (emphasis added). Sanchez-Ramos *et al.* acknowledges the importance of retinoic acid and BDNF pre-treatment, stating: "... the most likely explanation for the neurotropism or affinity of BMSC for

specific neuronal populations was due to pre-treating BMSC with retinoic acid and BDNF prior to grafting," (page 26, lines 7-10). Thus, it appears that the *in vitro* pre-treatments with retinoic acid and BDNF are important or essential for the Sanchez-Ramos method.

Therefore, the bone-marrow cells transplanted by Sanchez-Ramos were first subject to *in vitro* conditions that fundamentally change the properties of these cells. There is no evidence on record that such pre-treated cells can even form heterokaryons with Purkinje cells, as recited in claim 34. In fact, it is quite possible that such pre-treated cells are committed to neuronal development, such that they differentiate into Purkinje neurons without forming heterokaryons with pre-existing Purkinje neurons (though the data in Sanchez Ramos *et al.* must be approached skeptically given Sanchez Ramos *et al.*'s admission that false positives may result from X-gal staining). Notably, Sanchez-Ramos makes no mention of any heterokaryons. To the contrary, Sanchez-Ramos proposes that bone marrow-derived cells *differentiate* into Purkinje neurons. He states, "[t]hese results indicate that our treated BMSC contain pluripotent cells which *differentiated* into neurons," (emphasis added, page 25, lines 22-23). The Examiner appears to agree with this position on page 17 of the instant Office Action ("took on" the Purkinje neuron phenotype).

Thus viewed, the cited art, even if combined in the way the Examiner suggests, at best teaches that G-CSF can mobilize bone marrow cells (per Bodine *et al.*), and at least some such mobilized cells may cross the blood-brain barrier to enter the brain (per Eglitis *et al.*). But since there is no established nexus between such G-CSF mobilized bone marrow stem cells and the pre-treated cells in Sanchez-Ramos *et al.*, the combined art fails to teach all the limitations of the claimed invention (*e.g.*, the formation of heterokaryons of the mobilized bone marrow stem cells with Purkinje neurons).

At the least, in view of the cited art, one of skill in the art would have had no reasonable expectation that the G-CSF mobilized bone marrow stem cells can form heterokaryons with Purkinje neurons, since Sanchez-Ramos *et al.* is completely silent in that respect. Furthermore, one of skill in the art wouldn't even have had reasonable expectation that the G-CSF mobilized bone

marrow stem cells would behave similarly as the pre-treated Sanchez-Ramos *et al.* cells to differentiate into Purkinje neurons on their own.

The Examiner argues that "the preamble of claim 34 states an intended use of the process," (page 20). In fact, it is not only the preamble but the body of claim 34 that refers to heterokaryons. The body of claim 34 recites, in pertinent part, "wherein the agent induces mobilization of bone marrow cells which results in the formation of the Purkinje/bone marrow-derived heterokaryon in the nervous system of the individual."

The Examiner also argues that "claims 39, 41-44 describe an intrinsic effect upon administering G-CSF to patients having a disorder of Purkinje neuron deficiency, and hence even though this and other references do not teach the effect, it would occur upon administering G-CSF to a subject," (page 20). In essence, the Examiner makes an inherency argument in a 103 rejection. However, pursuant to MPEP 2141.02 V. "Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993)."

Additional examples of nonobviousness of a claim to a method of obtaining a benefit inherent in a prior art use are provided by *In re Adams*, 148 USPQ 743 (CCPA 1966). As described in "Anticipation by Inherency or Accident" by Dr. Karen Canady, "[i]n *Adams*, the claims were directed to a heat transfer method using aerating or foam nozzles to cool cans filled with hot food. The claims were rejected as obvious in view of the use of foam for heat transfer by fire departments or the use of aerated faucets for cooling plates in a kitchen sink. The Patent Office argued that heat transfer was inherent in both of these prior art operations. The court responded by acknowledging the inherency of heat transfer in the prior operations, but noted that patentability hinged on the unexpected and unsuggested increase in heat transfer efficiency and not on inherency."

As with *Adams*, even though the combination of Bodine *et al.* and Eglitis *et al.* might lead to the entry into brain of G-CSF stimulated bone marrow stem cells, and may inherently lead to the formation of heterokaryons, such a combination would not render the claimed method obvious, because, like in *Adams*, patentability of the claimed method "hinged on the unexpected and

unsuggested" benefit of heterokaryon formation. Note that Sanchez-Ramos *et al.* does not state or imply that heterokaryons could be formed since, as argued above, the Sanchez-Ramos *et al.* method purportedly teaches differentiation of pre-treated cells, and there is no evidence that such pre-treated cells can participate in heterokaryon formation. Thus, the cited art cannot be relied upon to establish "inherent obviousness" of the claimed invention *et al.*

Finally, Applicants note that, in making the enablement rejection, the Examiner suggests in the recent Office Action that little was known in the art about Purkinje/bone marrow-derived heterokaryons prior to Applicants' disclosure: "[i]n the instant case, using bone marrow cell mobilization therapy to promote formation of Purkinje/BMC heterokaryon and to treat neuronal deficiency is a novel concept presented by instant applicant, [and] little was known in the art about whether this idea was feasible, and the state of the art was such that three was no known means sufficient for producing a Purkinje/bone marrow-derived heterokaryon in an individual" (page 11 of the Office Action). Thus, it seems contradictory to argue on the one hand that the claimed invention is not enabled because of this alleged lack of knowledge in the art, and argue on the other hand that the claimed invention is obvious because one of skill in the art would have been able to piece together knowledge in the art to arrive at the claimed invention.

In conclusion, a *prima facie* case of obviousness has not been established based on the art cited. Reconsideration and withdrawal of this rejection on ground of 35 USC 103(a) is respectfully requested.

Claims 8-13 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Sanchez-Ramos *et al.* (WO99/56759) in view of Bodine *et al.* (Blood 1994; 84:1482-91), Eglitis *et al.* (US Patent 7,022,321), and Martinex-Murillo *et al.* (Neurosci 1993; 52:587-93).

The deficiencies of Sanchez-Ramos *et al.*, Bodine *et al.*, and Eglitis *et al.* are discussed above. Martinex-Murillo *et al.* do not remedy these deficiencies.

Thus, reconsideration and withdrawal of this rejection on ground of 35 USC 103(a) is respectfully requested.

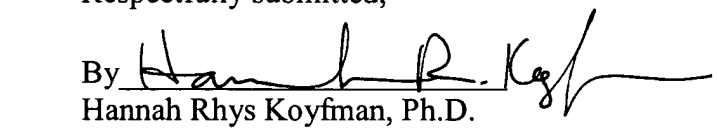
CONCLUSION

In view of the above remarks and amendments, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due with this response other than those itemized in the accompanying fee transmittal. However, if any additional fee is due, please charge our Deposit Account No. 18-1945, under Order No. **SUPP-P01-011** from which the undersigned is authorized to draw.

Dated: March 16, 2009

Respectfully submitted,

By 

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